

## **REMARKS**

Applicants have received and reviewed the Office Action dated December 31, 2008. By way of response, Applicants have amended claims 12, 14, 22 and 23 and added new claim 25. No new matter has been added. Claims 12-24 are pending.

Support for the amended claims and new claim 25 can be found throughout the specification, for example, at the originally filed claims.

Applicants submit the claims are now in condition for allowance and respectfully request a notice of allowance.

## **Objections**

The Examiner objected to claim 12 for containing informalities. Amended claim 12 defines both X and m after formula (II). Applicants have amended claim 12 to remove these informalities and respectfully request withdrawal of this objection.

## **35 U.S.C. § 103(a)**

Examiner rejects claims 12-21 under 35 U.S.C. § 103(a) over Johnson et al., WO 99/18065, in view of Tinsley et al., US 3,375,287. Applicants respectfully traverse this rejection.

Applicants submit the presently claimed invention is non obvious for at least the following reasons: 1) The Office Action has failed to recognize that the reaction in Johnson is two independent reaction steps, (a) the catalytic transformation of OXIME into ENAMIDE and (b) the catalytic hydrogenation of ENAMIDE into an AMINE through an AMIDE; 2) The presently claimed invention results in an unexpectedly high yield that is reliably produced for use in large scale industrial production; and 3) the catalyst to OXIME mole ratio of the presently claimed invention is only 0.001 to 30% versus a 2 mole ratio in Johnson. The shortcomings of the Johnson reference are not remedied by the secondary Tinsley reference.

The Office Action alleges Johnson teaches a process for the production of enamide derivative of formula 4, prepared by reaction of an oxime of formula 2, with a reducing metal M in presence of an acylating agent. The catalyst used is a complex of a transition metal  $M^{2+}$  and a chiral phosphine ligand. The Office Action emphasizes that the reaction temperature is at moderate temperatures = 75°C, with moderate to good yields (40-85% unoptimized) and in a high state of purity. Further, the Office Action alleges that Johnson exemplifies the synthesis of

N-(3,4-dihydronaphthalen-1-yl)-acetamide using Fe as the catalyst.

The Office Action admits the difference between Johnson and the presently claimed invention is:

- (i) Johnson et al fail to teach applicant's particular hydrogenation catalyst metal;
- (ii) Johnson et al fail to teach particular form of catalyst;
- (iii) Johnson et al fail to teach hydrogen pressure and with the particular mineral salt.

The Office Action alleges (i) and (ii) are obvious because Tinsley teaches the equivalency of catalytic reducing metals with the combination of various compounds used for isomerization reactions which include Ni, Pd, Pt, Rh, Ir, Fe and Ru.

The Office Action alleges (ii) and (iii) are obvious because a skilled artisan would optimize the particular form of the catalyst, the use of hydrogen pressure and the particular mineral salt during the optimization process. The Office Action notes Applicant does not show any unusual and/or unexpected results for the limitations stated. Further, the Office Action Notes that the prior art provides the same effect desired by Applicant, the production of enamide derivatives from oximes. Applicants respectfully disagree.

First, Examiner has not recognized that Johnson is two different reaction steps, namely:

A) A first step of catalytic transformation of OXIME into ENAMIDE, from the chemical structure (2) to the chemical structure (4) (page 4, lines 1 to 10).

B) A second step in which it is performed the catalytic hydrogenation of ENAMIDE into (in particular CHIRAL) AMIDE and then into a (in particular CHIRAL) AMINE, see the two sequences of steps from the enamide of formula 4 to the amide of formula 5 and then the amine of formula 6 on page 4 of Johnson.

Applicant notes that there is a fundamental difference between the first step A) of catalytic transformation of OXIME into ENAMIDE and the second step B) of catalytic hydrogenation of ENAMIDE into AMIDE or AMINE.

Johnson confirms this at page 5, line 14 and lines 20-22 where in the first step of catalytic transformation of OXIME into ENAMIDE, it is required the specific use of iron as reducing metal M1 (see page 5, line 14) with provides the obtention of a mixture of monoacetyl and diacetyl (assuming acetic acid is used).

The Office Action alleges that Johnson discloses a catalyst that is a complex of a transition metal  $M^{2+}$  and chiral phosphine ligands, referring to Johnson claim 2 and the examples

Applicants respectfully submit that Johnson's use of catalyst is relating to step B which is the hydrogenation of the enamide into the (chiral) amide or amine. Further, this specific hydrogenation of the enamide to amide or amine is step C in each one of the examples of Johnson. Thus, Johnson does not use a complex of the transition metal  $M^{2+}$  and a chiral phosphine ligand in the first step of isomerization of the oxime into the enamine.

Second, Johnson alleges to produce a moderate to good yield (40-85%) during step (A); however as it appears from the examples, the yield is highly variable, unpredictable and therefore unreliable. For instance, in example 2B the yield is only of 50%; in example 4B the yield is only 43% (page 9, line 26); in example 5, relating to  $\alpha$ -tetralone, the yield is only of 54% (page 10, line 28).

By contrast and unexpectedly, the presently claimed invention has a **high yield that is reliable**. Further, the presently claimed invention also results in an excellent chemical purity under a reproducible process (page 1, paragraph [0008-0007]) and the process is usable on a large scale industrial production of amine derivatives (paragraph [0008] of the application as published under US 2007/0129573).

Finally, Johnson et al uses a molar proportion of the catalyst which is twice that of the oxime. This is apparent from all of the Johnson examples:

Example 1B: oxime 0.66 mole; iron powder 1.33 mole;

Example 2B: oxime 286.5 millimole; iron powder 573 millimole;

Example 3B: oxime 30.6 millimole; iron powder 61.2 millimole

Example 4: oxime 25.9 millimole; iron powder 51.5 millimole

Example 5 relating to  $\alpha$ -tetralone: oxime 279 millimole ; iron powder 558 millimole;

Example 6: 1- oxime 34 millimole ; iron powder 68 millimole (note a yield of only 36%)

Example 7B : oxime 0.7 mole ; iron powder 1.4 mole, (yield 63%)

In the presently claimed invention, the heterogenous catalyst is preferably used in the form of an oxime or metallic and may be supported in a suitable carrier and is used in the amount of 0.001 to 30% mole based on the oximes derivative. This constitutes unexpected technical results which support unobviousness of the invention over the prior art.

For contrast, Applicants compare Johnson's example 5 with the present inventions example 3. In example 5b of Johnson et al, the yield is of 54% with use of iron powder with a mole ratio of catalyst to substrate of 2/1. By contrast, example 3a of the present invention has a

84% yield with Rh/C with a weight ratio of only 4% of catalyst as compared to the oxime. In example 3b, the yield being of 79% with Ir/C with the same weight ratio of catalyst of only 4% with regard to the oxime. Therefore, the presently claimed invention provides an unexpected increase in yield and utilizes non obvious difference in catalyst to oxime ratio.

The Office Action cites Tinsley et al for the premise of equivalency of catalytic reducing metals, with the combination of various compounds, used for isomerization reactions, including Ni, Pd, Pt, Rh, Ir, Fe and Ru by making reference to columns 4, lines 1-2 of Tinsley.

In view of the above argument, Applicants further submit that the combination of Tinsley with Johnson is not obvious for at least the following reasons:

First, Applicants submit that the combination of Tinsley with Johnson is not obvious for the skilled person in the art, absent hindsight reconstruction with knowledge of the present invention which is not acceptable under US Patent Law and Practice.

In addition, and in an essential manner, the teaching of Tinsley has to be limited to processes for isomerizing ethylenically unsaturated compounds possessing cycloaliphatic nucleus (see Tinsley title and column 1, lines 55 to 60 where Tinsley points discloses that the ethylenically unsaturated compounds which can be employed in the process of this invention typically are composed solely of carbon and hydrogen, the cycloaliphatic nucleus having up to 16 carbon atoms in said nucleus ... and at least one migratable ethylenic bond.)

This is clearly not applicable to oximes which contain two heteroatoms namely nitrogen and oxygen, the nitrogen atom bearing the unsaturated bond (see formula II in claim 12 of present application).

Thus, Applicants submit it would not have been obvious to combine Tinsley, which relates to a different type of unsaturated compounds composed solely of carbon and hydrogen, with the Johnson reference relating to oximes.

Further, Examples 1 to 24 of Tinsley relate to vinylcyclohexene or vinyl cyclohexane (examples 1 to 3, 15, example 24), 1,5-cyclooctadiene (examples 4 to 10, 16 to 18, 20, 21 to 23), or 4-methylcyclohexene (example 12-14). All the Tinsley examples are relating to similar compounds which are entirely different from oximes.

Applicants submit it is apparent that Tinsley is relating to the isomerization of compounds which are entirely different from oximes and in addition, Tinsley is limiting the validity of his process to ethylenically unsaturated compounds which are composed solely of

carbon and hydrogen (column1, lines 55 to 60).

Applicants submit the combination of Johnson with Tinsley to arrive at the presently claimed invention is not obvious. Further, the presently claimed invention unexpectedly discovered a process that results in a high yield that is reliably produced for use in large scale industrial production. Applicants submit Examiner has failed to establish a *prima facie* case of obviousness and respectfully request withdrawal of this rejection.

#### Rejoinder of Claims 22-24

In the Office Action, the Examiner has maintained that claims 22 to 24 are withdrawn because the method of manufacture of an amine or amide compound is entirely different from that of process claims 12 to 21. Applicants respectfully traversed for the following reasons.

First, the present application is a national US phase of a PCT application for which the unity of invention was recognized which is directly applicable to US national examination. Examiner takes the position that there was no common technological feature between claim 22 and claim 12. Applicants submit amended claim 22 now recites the first exact hydrogenation/isomerization reaction as set forth in method claim 12.

In view of this, there is clearly a common feature between process claim 12 and method claim 22, namely the step of preparation of the enamide by performing hydrogenation/isomerization reaction as defined in claim 12. This is all the more accurate that the patentable part of the invention as defined in claims 22 to 24 is the patentable step of performing the hydrogenation/isomerization of the oxime of formula (II) with the acyl derivative of formula (III).

Claim 22 has been further amended to recite the preparation of an enamide selected from that of formula (II E) or the individual compounds which are set forth in previously pending claim 24.

As a matter of fact, only inden acetamide was falling under the scope of structure of formula (II E), whereas the "naphthalenyl acetamides and the phenyl-cyclohex-1-enyl acetamide were out of the scope of the formula (II E).

In view of this, the new formulation of claim 22 is generic for preparation of all the compounds under formula (II E) and the individual compounds naphthalenyl and cyclohexenyl.

Claim 24 has been maintained unamended since it claims the individual compounds of the examples.

It is also further observed that in the amended version of claim 22, other amendments were made in the reaction definition. As a matter of fact, it is the hydrogenation of the enamide which provides the hydrogenated compound whereas the hydrogenation/isomerization reaction prepares the enamide in particular of formula (II E), and not a saturated compound which is obtained after the further hydrogenation step to prepare an amide or an amine which, when the hydrogenation is asymmetric as recited in claim 23, it is obtained a chiral amide or amine. Therefore, claim 23 has also been amended to precise that the asymmetric hydrogenation provides the obtention of a chiral amide or amine.

Applicants respectfully request claims 22 to 24 be rejoined in their amended form.

#### Summary

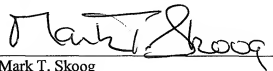
In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Please charge any additional fees or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,

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